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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,391	MARTH ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6-21-05 and 2-17-05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communications filed 2-17-05 and 6-21-05.

Claims 36-49 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6-21-05 has been entered.

The declaration under 37 CFR 1.132 filed 6-21-05 is insufficient to overcome the rejection of claims 36-49 based upon as set forth in the last Office action for the reasons stated in the rejection set forth below as well as those provided in addressing Applicant's arguments below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Applicant's arguments with respect to claims 36-49 have been considered but are largely moot in view of the new ground(s) of rejection set forth below. These arguments are addressed below as they pertain to the new rejection of record.

New Rejections

Claims 36-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of systemic C2 GlcNAc T^{Δ} or conditional C2 GlcNAc T^{F} homozygous mice using Cre-loxP recombination, whereby a deficiency of C2 GlcNAc transferase activity and a deficiency of core 2 O-glycan synthesis were observed in isolated null mouse splenocytes, does not reasonably provide enablement for methods of inhibiting inflammatory responses in a mammal, or for methods of modulating binding of a first myeloid cell to a second myeloid cell or to an endothelial cell in an organism comprising the administration of a compound that modulates the synthesis of a core 2 oligosaccharide or the administration of a compound that inhibits the activity of a core 2 GlcNAc transferase in an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of inhibiting an inflammatory response in a mammal and/or modulating binding of a first myeloid cell to either an endothelial cell or

to a second myeloid cell comprising the administration of a compound that inhibits the activity of a core 2 GlcNAc transferase, or that binds to or modulates the synthesis of a core 2 oligosaccharide.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate that the delivery to a target cell in vitro or in vivo of candidate inhibitory molecules, including polypeptides and/or small molecules, is energy dependent and may require the presence of specific proteins that serve as receptors and or channels to provide the intracellular concentrations of small molecule inhibitors required for inhibition. Derossi et al teach the ability of antennapedia homeodomain to translocate through biological membranes, but this ability is highly sequence dependent, and illustrates that delivery of polypeptides to target cells in vitro or in vivo is a rate limiting step for cell targeting and entry for most polypeptides (see D. Derossi et al. J. Biol. Chem. 269(14): 10,444-10,450, especially the abstract on p. 10,444, last paragraph of the introduction on p. 10,444; first full paragraph on p. 10,450: "Other polypeptides that cross biological membranes are those destined, after synthesis, to specific intracellular compartments such as the endoplasmic reticulum or the mitochondria... Passage through these intracellular membranes is energy-dependent and requires the presence of specific proteins that serve as receptors and/or channels. However, even in this rather well studied system, the actual mechanism of

importation is not yet completely understood." For specific requirements of other, specialized polypeptides involved in cellular membrane penetration, see M. Pooga et al. FASEB J. 12: 67-77 for a discussion of the remarkable properties of transportan; see also G. Elliott et al, Cell 88 : 223-233 for the distinguishing features of Herpes virus structural protein and its role in intercellular trafficking).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting an inflammatory response in a mammal, or of modulating the binding of a first myeloid cell to either an endothelial cell or a second myeloid cell comprising the administration of any compound that inhibits the activity of a core 2 GlcNAc transferase, or any compound that binds to or modulates the synthesis of core 2 oligosaccharide in an organism. The instant disclosure teaches the production of systemic C2 GlcNAc T^{Δ}, or conditional C2 GlcNAc T^{F}, homozygous mice using Cre-loxP recombination. The specification teaches a loss of C2 glcNAc transferase activity, and a deficiency of core 2 O-glycan formation in isolated splenocytes from these null mice, as well as a loss of the B220 epitope in splenocytes in mice lacking C2 GlcNAc transferase activity. The specification also teaches the absence of 1B11 antibody binding to myeloid cells in mice lacking C2 GlcNAc transferase activity. One skilled in the art would not accept on its face the examples given in the specification of generating systemic C2 GlcNAc T^{Δ} or conditional C2 GlcNAc T^{F} homozygous mice using Cre-loxP recombination as being correlative or representative of the successful inhibition of an inflammatory response in a mammal or

the successful modulation of binding of a first myeloid cell to either an endothelial cell or a second myeloid cell comprising the administration of any compound that inhibits the activity of a core 2 GlcNAc transferase, or that binds to or modulates the synthesis of core 2 oligosaccharide in an organism in view of the lack of guidance in the specification and known unpredictability associated with the inhibition of glycosyl transferases or inhibition of oligosaccharide synthesis in vitro or in vivo comprising the administration of sugar substrate analogs or other potentially inhibitory compounds. The successful generation of null mice is not representative of the ability to successfully target and inhibit C2 GlcNAc transferase in vivo comprising the administration of inhibitors. It must also be stressed that in vitro results cannot be extrapolated to in vivo inhibition and subsequent treatment effects. In vivo results require undue experimentation, and cannot be generalized from a test tube (or cell culture) to an organism.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to methods of inhibiting an inflammatory response in a mammal and/or modulating binding of a first myeloid cell to either an endothelial cell or to a second myeloid cell comprising the administration of a compound that inhibits the activity of a core 2 GlcNAc transferase, or that binds to or modulates the synthesis of a core 2 oligosaccharide. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring core 2 GlcNAc transferase whereby core 2 glycan biosynthesis is inhibited in vivo and treatment effects are provided for inflammatory

responses in a mammal, and whereby the binding of a first myeloid cell to either an endothelial cell or a second myeloid cell is inhibited in a mammal following administration of such inhibitory compounds. Since the specification fails to provide any particular guidance for the targeting and inhibition of core 2 GlcNAc transferase, or for the modulation of the synthesis of core 2 oligosaccharides using inhibitory compounds in an organism, and further whereby treatment effects are provided inflammation, and since determination of these factors (e.g. the targeting and inhibition of core 2 GlcNAc transferase using inhibitory compounds) is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Applicant's arguments and declaration filed 6-21-05 have been fully considered but they are not fully persuasive. Applicants argue that the full scope of the claims is enabled for several reasons. Applicants argue, for instance, that it is well known to those skilled in the art that gene target elimination in null mice is very predictive of the effects of using inhibitors that directly interact with the respective gene product in vivo. Applicants argue further that, as evidence of such predictability, excellent correlation between phenotypes in null mice and known drug efficacy exist. Applicants are correct that correlations have been found to exist between a phenotypes observed in null mice and the efficacy of various drugs. The Zambrowicz et al reference provided by Applicants provides an overview of correlations that have been identified between such ablation experiments and drug development, as well as discussing potential gene targets and drug candidates now in the pipeline. Zambrowicz states that "Gene KO

technology has proven to be an effective method for modeling drug efficacy and determining the physiological functions of mammalian genes." (bridging paragraph, pp. 563-564). Contrary to Applicants' assertions, however, providing a correlation between phenotypes and the ablation of a target gene is not the same as providing that phenotype by administration of a drug or drug candidate, absent further experimentation. Ablation experiments have been used to define gene function and identify candidate targets for drugs, but the identification of a gene or molecular target is not correlative of the ability to achieve the phenotype observed (*e.g.* in an ablation model) using a candidate drug. The efficacy of the drug's ability to reproduce that particular phenotype observed in an ablated animal is derived empirically, not extrapolated from what happens when a gene is knocked out in an ablated animal.

Many investigators involved in the development of antisense technology as a treatment approach for many diseases have written about the unpredictability of gene targeting by administering agents to an animal in vivo. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (A. Branch, Trends in Biochem. Sci. 23: 45-50, document "BA" in IDS filed 11-17-03, *see* entire text for Branch; S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using oligonucleotide based approaches

Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: AIt is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the Aimportant and inordinately difficult challenges of the delivery of therapeutic oligonucleotides to target cells).

Applicants argue that sufficient correlation exists to extrapolate in vitro results to in vivo efficacy. Contrary to Applicants' assertions, one cannot extrapolate in vitro results to in vivo success. The ability to inhibit an enzyme's activity in vitro is not

predictive of the ability to inhibit it in vivo, and further whereby treatment effects are provided. The inhibitor concentrations necessary for enzyme inhibition are more easily obtained in a test tube than in appropriate target cells in vivo. Proper formulations and modes of delivery of a particular inhibitor required to achieve the requisite inhibitor concentrations require undue experimentation beyond that taught in the instant disclosure. And one cannot extrapolate the success of a different drug or compound, acting on a different target, to the instant application.

Applicants argue that one skilled in the art would readily accept the fact that inhibition of C2GlcNAc transferase protein in vivo would provide the claimed effect - of inhibiting an inflammatory response in a mammal - because the transferase activity has been characterized extensively and the association between selectin receptors and leukocyte extravasation, etc has been shown. Applicants are correct that, if C2GlcNAc transferase protein were sufficiently inhibited in vivo, an inflammatory response would likely be inhibited in a mammal. The unpredictability lies not in predicting the phenotype - should the transferase be inhibited – the unpredictability lies in determining whether effective inhibitor concentrations can be obtained in vivo to inhibit this enzyme, following administration of the drug candidate. The phenotypes achieved in an ablated model represent a model response when a gene has already been ablated. But the question to be answered is whether any proposed inhibitors can provide treatment effects upon administration in vivo. While the ablation models identify gene targets and identify potential candidates for therapy, they do not provide the requisite guidance that such

proposed candidates in fact provide treatment effects claimed. For these reasons, the enablement rejection is maintained.

Related Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

King et al USPN 6,131,578 teaches increased expression of core 2 GlcNAc transferase expression in cardiomyocytes harvested from spontaneous autoimmune-caused diabetic nonobese diabetic (NOD) mice. King is distinguishable from the instant invention because King teaches the increased expression of core 2 GlcNAc transferase activity in cardiomyocytes, but does not provide any in vitro or in vivo inhibition of transferase activity using inhibitory molecules. King teaches a correlation between increased transferase expression under diabetic conditions in a mouse model, and teaches the in vitro transfection of recombinant core 2 GlcNAc transferase in Cos cells.

Nakamura et al (J. Biol. Chem., 273(41) : 26,779-26,789 (1998)) teach decreased expression of core 2 mRNA transcript in KM3 cells following TPA treatment, in turn reflecting a decrease in enzyme expression/enzyme activity levels (see abstract on p. 26,779, last paragraph of the introduction on p. 26,780, figure 6 on p. 26,786, bridging paragraph pages 26,786-26,787). Nakamura is distinguishable from the instant invention because Nakamura et al teach decreased core expression, not enzyme activity, upon induction of cellular differentiation using TPA.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ∋ 1.6(d)). The official fax telephone number for the Group is **703-872-9306, or after July 15, 2005, the new fax telephone number is 571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
8-20-05